



Evidence of Clinical Effectiveness and Data Requirements

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Outline

- Assessing Clinical Effectiveness
 - Adequate and well controlled trials
 - Endpoints of direct clinical benefit
- Data Requirements
 - Content
 - Format

Laws, Regulations, Guidances



- Statutes - Congressional bills signed into law
 - Federal Food, Drug, and Cosmetic Act
- Regulations – implementing standards for statutes
 - Code of Federal Regulations e.g. 21 CFR sec. 314.50
- Guidances - Informal agency statements that represent current agency thinking, not legally binding
 - <http://www.fda.gov/cder/guidance/index.htm>

The Food, Drug and Cosmetic Act of 1938

Required premarket notification.

Required a demonstration of safety for approval.

Basis of refusal:

- (a) **did not include ALL tests reasonably applicable** to show whether drug is safe when used under proposed labeling
- (b) testing shows drug unsafe or do not show that it is safe
- (c) information submitted or any other information available are insufficient to determine whether safe
- (d) labeling is false or misleading in any particular

Keyfauver Harris Amendments 1962

1. FDA had to actively grant approval before a drug could be marketed
2. Requirement to study drugs under an IND; informed consent
3. The effectiveness requirement:
Substantial evidence that the drug will have the effect it purports or is represented to have under proposed **labeled conditions of use.**

Drug Regulation History

- 1970s drug lag
- 1980s public health needs – clamor for access to investigational drugs (HIV epidemic)
- PDUFA 1992 – specific timelines S/P 10/6 months
- FDAMA 1997 – fast track for drugs for serious disease AND fill an unmet need
- FDAAA 2007– authorities for safety assessment
- FDASIA 2012 – generic drug/medical device UFAs
GAIN, QIDP, breakthrough, standards mandates, etc



LABELING 21CFR 201.56-57

Labeling must bear adequate directions for use
and may not be false or misleading

Very critical to support requirements for dose-
response and individualization information
(21 CFR 314.50 mandates for safety and
effectiveness – age, gender, [race])

Aims of NDA/BLA review

- Assess a biologic for purity, identity, safety and potency
- Assess a drug to be safe and effective

Clinical Effectiveness

Substantial evidence consists of adequate and well-controlled investigations **including** clinical investigations...on the basis of which it could be concluded that the drug will have the effect it is represented to have under the **conditions of use proposed in labeling**.

FDAMA 1997 – allow 1 study in certain circumstances
Effectiveness – “**clinically meaningful**” added in court

Regulations that affect an NDA Submission

21CFR 314.50: Content & Format of an Application

21CFR 314.126: Adequate & Well-Controlled Studies

21CFR 314.500: Accelerated approval (use of
surrogate endpoints and approval
with restrictions)

Adequate and Well-Controlled Studies s 21 CFR 314.126

Well controlled studies of adequate design must show effectiveness, ordinarily a STATISTICALLY significant effect on a CLINICALLY meaningful endpoint, usually replicated, as a basis for approval.

Robert Temple

Adequate **AND** Well-Controlled Studies

Principle:

Trial should measure drug effect, not spontaneous change or influence of unacknowledged bias

Therefore, trials should be of ADEQUATE design where the CONTROL group is essentially identical to test group except exposure to test agent

AWC trials minimize bias favoring either treatment group in how test and control are selected, treated, observed or analyzed

Bias reduction	pre-study,	during	and post study
	DESIGN	CONDUCT	and ANALYSIS

ADEQUATE DESIGN

- PRE-define a win, and in some cases, by how much (endpoint, timing, analytic population, SAP)
- Design permits quantitative comparison with the control (powered)
- Adequate exclusion/inclusion
- Randomization procedures
- Baseline comparability of treatment groups
- Adequacy of blinding/ allocation concealment

Well-Controlled Studies

21 CFR 314.126

- Placebo control
- No treatment concurrent control
- Dose-response control
- Active Control
- Historical Control

Measuring Drug Effect (AWC)

SUPERIORITY studies allows a direct measure of drug effect, but not always feasible to conduct (superiority to placebo may not be ethical or superiority to active control may not be achievable).

Drug-placebo=attributable effect (M1)

If the trial intends to show similarity (NONINFERIORITY) of the test and control drugs, the report should assess the ability of the study to have detected a difference between treatments, should one exist.

Drug = comparator with known drug effect (Drug-P)



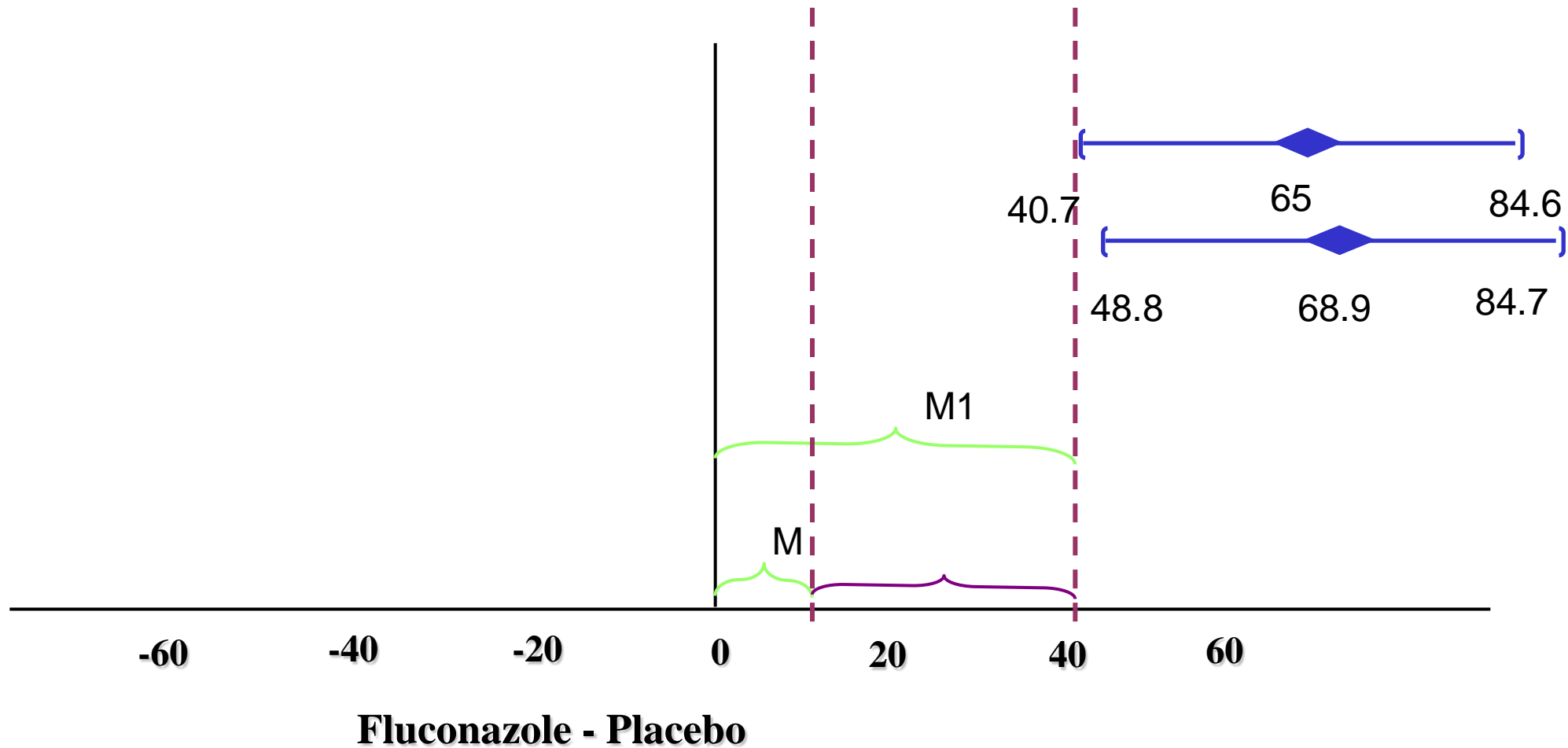
Noninferiority Trials

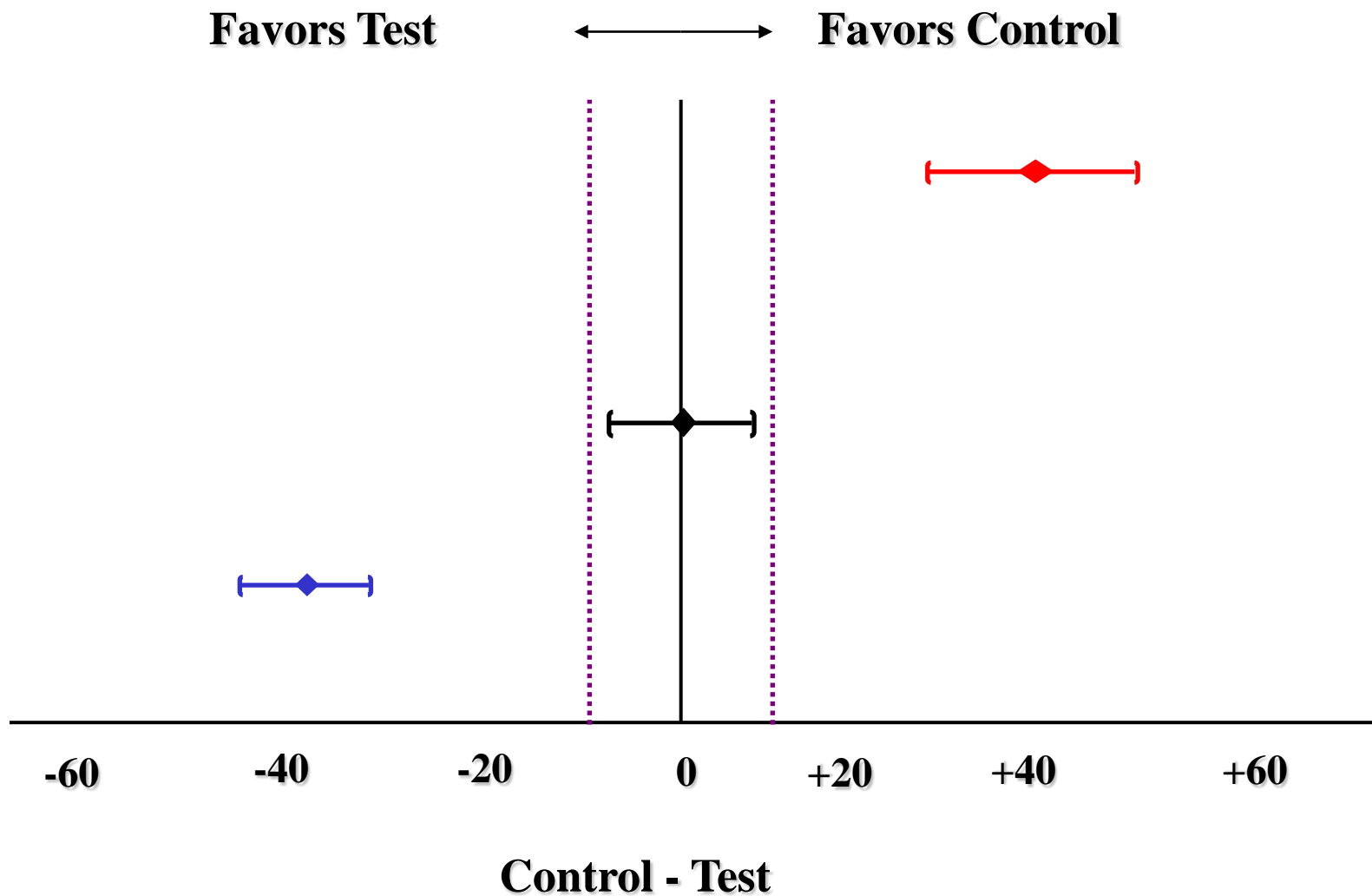
Desire to use equivalence is understandable: seems sensible to compare new and old effective therapy. Avoids exposure to ineffective treatment.

Fundamental distinction between trials intended to show a difference and trials intended to show similarity; latter pose major problems of interpretation.

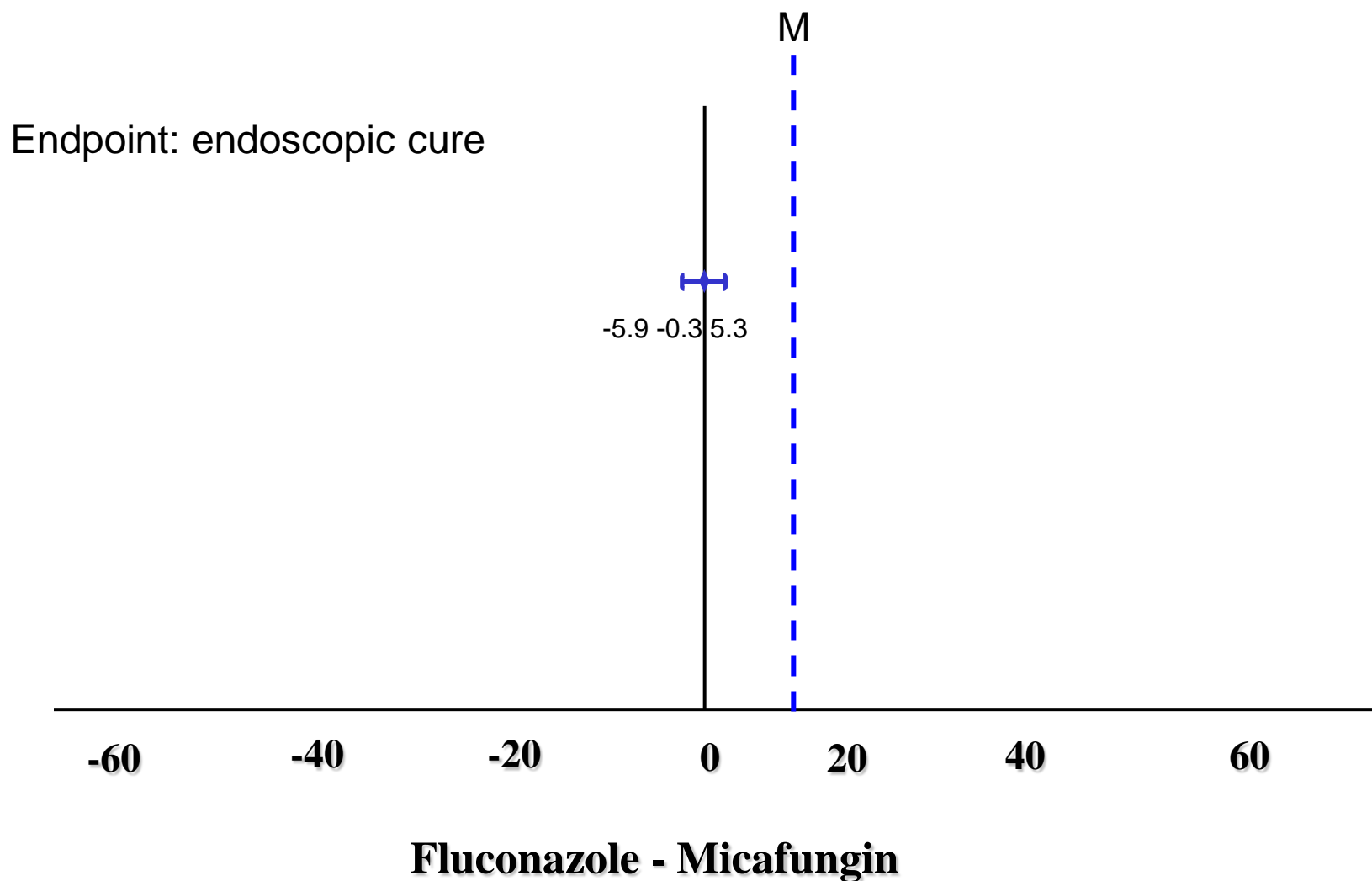
Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective.

Treatment Effect of Fluconazole in EC





Noninferiority of Micafungin to Fluconazole in EC



ENDPOINTS: Definition & characteristics

Distinct and measurable characteristics used to assess the outcome of therapeutic interventions



21 CFR 314.126(b)(6) “The methods of assessment of subjects’ response are well-defined and reliable.”

Well defined “treatment benefit = effect on how a patient survives, feels or functions. ..other measures that do not capture these are surrogate measures of benefit”

p33 // www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282

Endpoints – consider implications in context of study design

- Composite Endpoints – multiple ways to win
 - When outcomes are discordant
 - Which component drives a win
 - Which component is sensitive to drug effect
- Measuring Endpoints
 - Patient Reported Outcomes, Biomarkers
- Methods of Collection
 - Standards enhance replication, balance with flexibility

Quantity of Evidence Needed to Support Effectiveness

Congress intended to require at least two adequate and well-controlled studies, **each convincing on its own**, to establish effectiveness.

“In most drug development programs, the need to find an appropriate dose, to study patients of greater and lesser complexity or severity of disease, to **compare the drug to other therapy**, to study an adequate number of patients for safety purposes, and to otherwise know what needs to be known about a drug before it is marketed will result in more than one adequate and well-controlled study upon which to base an effectiveness determination.”

“Guidance on Clinical Effectiveness”

One Adequate & Well Controlled Study

Relied on single excellent multicenter study with statistically strong finding, or where there was an important clinical benefit, (for example, such clear superiority in mortality), making a confirmatory study difficult to conduct on ethical grounds.

SO, A VERY HIGH BAR to conduct a SINGLE AWC study.

Regulatory Flexibility : Clinical Effectiveness Guidance

Extrapolation (no efficacy studies of required) e.g. bioequivalence, pediatric studies

One adequate and well controlled study + independent substantiation
(CONFIRMATORY study)

- Efficacy study of different dose, regimen or form
- Efficacy in another disease phase
- Efficacy in another population
- Combination or monotherapy
- Efficacy in a closely related disease
- Efficacy in unrelated disease but where purpose is similar
- Efficacy in different endpoints
- Pharmacologic/ pathophysiologic correlation

One study (NO CONFIRMATORY DATA NEEDED)

- multicenter study - no single site provides large fraction of patients & drives the result & consistency across study subsets is seen - demographic, severity etc
- Multiple studies in a single study (Factorial studies)
- Multiple endpoints involving different events
- Statistically very persuasive finding

Guidance: Concepts for Expedited Programs for Serious Conditions

Serious Condition: defined in Accelerated Approval Regulations (57 FR 58942, 1992) as conditions that as “*a matter of clinical judgment.. impact... survival, day to day functionality, or likelihood that if left untreated progress to more serious one*” [21 CFR312.300(b)(1)]. Life threatening as defined in 21 CFR 312.81(a) would also be serious. Consistent with accelerated approval, fast track designation, expanded access of investigational drugs for treatment use.

Eligible products- “*intended to have an effect on a serious aspect of a condition, such as a direct effect on a serious manifestation or symptom of a condition, or other intended effects, including:*

- *A diagnostic product intended to improve diagnosis or detection of a serious condition that lead to improved outcomes*
- *A product intended to improve/prevent a serious treatment-related side effect (e.g., serious infections from immunosuppression)*
- *A product intended to avoid a serious adverse effect associated with available therapy for a serious condition (e.g., less cardiotoxicity than available cancer therapy)”*

Guidance: Concepts for Expedited Programs for Serious Conditions

Unmet need = treatment or diagnosis not addressed ADEQUATELY by available therapy, immediate need for a defined population or “*a longer term need for society*” (development or resistance in antibacterial drugs)

Existing or available therapy = approved or licensed in the United States for the same indication being considered for the new drug AND is relevant to current US standard of care (standard of care) for the indication, “*only in rare cases will a treatment that is not approved ...or is not FDA-regulated (e.g. surgery) be considered available therapy. (This) constitutes available therapy when the safety and effectiveness of the use is supported by compelling evidence, including evidence in published literature*” (e.g cancer). Recommendations from authoritative scientific bodies based on AWC or other “reliable” information and consultation with SGEs can inform US SOC.

<https://www.federalregister.gov/articles/2013/06/26/2013-15250/draft-guidance-for-industry-on-expedited-programs-for-serious-conditions-drugs-and-biologics>

*superceded Guidance for Industry: Fast Track Drug Development Program –Designation, Development and Review

Guidance: Concepts for Expedited Programs for Serious Conditions

A range of potential advantages beyond those shown in head to head comparisons will be considered - Even when not shown to have a n efficacy or safety advantage – *“a novel mechanism of action with a well-understood relationship to the disease pathophysiology. When a reasonable basis for concluding that a significant number of patients may respond differently to the new drug compared to available therapy may be a basis for this designation. For example, mechanistic diversity, even without a documented efficacy or safety advantage, could be advantageous in disease settings in which drugs become less effective or ineffective over time.”* As well it is preferable to have more than one treatment approved under accelerated approval regulations because benefit may not be verified in confirmatory trials for already approved products.

Covers the following programs: Fast Track Designation, Accelerated Approval, Breakthrough Designation

<https://www.federalregister.gov/articles/2013/06/26/2013-15250/draft-guidance-for-industry-on-expedited-programs-for-serious-conditions-drugs-and-biologics>

*superceded Guidance for Industry: Fast Track Drug Development Program –Designation, Development and Review

Fast Track

- FDAMA 1997 - process
- Drugs for serious disease AND fill an unmet need (Superior effectiveness, avoid serious side effects, improve diagnosis, reduce toxicity)
- Can be requested at any time during development, respond in 60 days
- Meetings, written correspondence, **eligibility** (not guarantee) for accelerated approval and rolling review, dispute resolution

Accelerated Approval

21 CFR 314.500

Approval based on a surrogate endpoint “that is **reasonably likely**, based on epidemiologic, therapeutic, pathophysiologic, or other evidence to **predict clinical benefit**”.

Conditions:

1. Serious or life-threatening illness
2. Meaningful benefit over existing treatments
3. Requirement to study the drug post-approval to “verify and describe its clinical benefit”.

Priority Review

- 1992 PDUFA FDA agreed to goals for drug review times
 - Standard review = 10 month clock
 - Priority review = 6 month clock
- Criteria:
 - Increased effectiveness in treatment, prevention, diagnosis,
 - elimination or reduction of treatment-limiting drug reaction,
 - **documented** enhancement of patients willingness or ability to take the drug according to required schedule and dose
 - safety & effectiveness in new subpopulation, ex children

Subpart H Accelerated Approval

- 1992 (21 CFR 314.500) regulation
- “Reasonable likely to predict” vs “survives, feels or functions”
- Surrogate vs direct clinical benefit; studies need to be AWC, needs confirmatory studies
- If confirmatory studies demonstrate direct clinical benefit, , traditional approval is granted, could lead to removal

Requirements 21 CFR 314 Subpart I

- (1) *Postmarketing studies.*
- (2) *Approval with restrictions to ensure safe use.*
 - (i) Restricted distribution to certain facilities/ trained health care practitioners
 - (ii) Distribution conditioned on performance of specified medical procedures,
 - (iii) Distribution conditioned on specified recordkeeping requirements.
- (3) *Information to be provided to patient recipients.*

labeling must explain that, for ethical or feasibility reasons, the drug's approval was based on efficacy studies conducted in animals alone and must give the drug's indication(s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information

Guidance/Advice

Written Guidances

Open Advisory Committee meetings

Availability of reviews after drug is
approved

Critical Guidance

1. ICH E3 “Structure and Content of Clinical Study Reports” reporting an important trials and integrated analyses of the efficacy and safety data, which are required under 314.50
2. E4 - Dose-Response Information to Support Drug Registration
3. E5 - Ethnic Factors (Really, what additional data should be requested if submitted data are extra-regional)
4. E6 - GCP's
5. E9 - Statistical Principles for Clinical Trials
6. E10 – Choice of Control Group
7. E-14 – Clinical Evaluation of QT/QTc
8. Clinical Evaluation by Therapeutic Category (Indication Specific)
9. Special Population, Genomic

Content and Format of an Application (21 CFR 314.50), ICH Common Technical Document

Module 1

- (1) application form
- (3) annotated text of proposed labeling
- (3) table of contents

Module 5

- (1) human pharmacokinetics
- (2) microbiology
- (3) clinical data
- (4) statistical section
- (7) pediatric use
- (8) CRF and CRT

<http://www.fda.gov/cder/regulatory/gov>

Clinical Section 21 CFR 314.50

Design
Conduct
Analysis

1. Description and analysis of .. every controlled study, including protocol and statistical analysis, .. sufficient reports of everything .. pertinent to safety and effectiveness from any source
2. Integrated data summary of substantial evidence of effectiveness and evidence to support dosage and administration, modifications for subgroups (pediatrics, geriatric, renal failure)
3. Safety summary & updates (4 months prior to approval) of with all available information (animal data, adverse effects, drug-drug interactions)

Clinical Section (continued)

4. Case report forms for deaths and discontinuations due to AEs (thought drug related or not). Others on request. Prior to 1985, all CRFs required
5. Case report tabulations. (replaced “all CRFs”)
All data from well-controlled studies
All data from earliest clinical pharmacology studies
Safety data from other studies

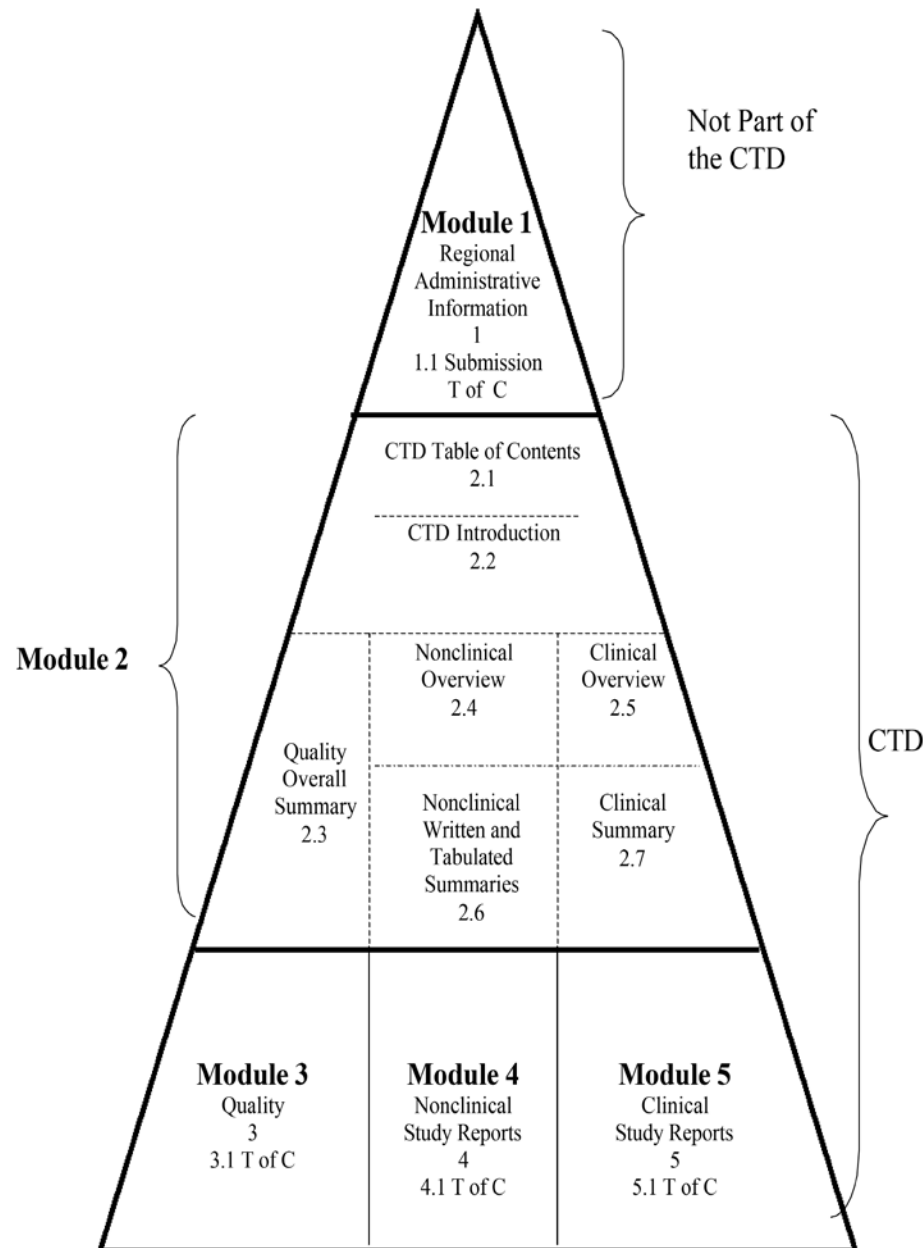


Data = Information = Knowledge = Understanding

Common Technical Data Format

Modules

- M1: Administrative Information
- M2: Summaries
- M3: Quality, i.e.: CMC
- M4: Non-clinical Studies
- M5: Clinical Trials



Modules M1 and M2

- **M1: Administrative Information**
 - Cover letter (1.2)
 - Administrative information (1.3)
 - Meetings (1.6) minutes of Agency-Sponsor interactions
 - Special Protocol Assessments (1.8); may also be in (1.6)
 - Annual Reports (1.13) especially if marketed elsewhere
 - Labeling (1.14)
- **M2: Summaries (all disciplines)**
 - Clinical overview (2.5)
 - Clinical summary (2.7)
 - Summary of Clinical Safety (2.7.4) - not the ISS
 - Summary of Clinical Efficacy (2.7.3) - not the ISE

Module M5

M5: Clinical Study Reports

- Tabular listing of clinical studies (5.2)
- Protocols and amendments (5.3.5.1.4)
- Case Report Forms (CRFs) (5.3.5.1.24)
- Clinical Trial Reports (CSRs) (5.3.5.1.3)
- Integrated Summary of Safety (ISS)
- Integrated Summary of Efficacy (ISE)
- Datasets (5.3.5.1.25)
 - Electronic datasets (5.3.5.1.25.3)
 - Define files (5.3.5.1.25.3.3)

Guide to submission and analyses
describe & document files
select analyses, key variables
handling missing data

Document study conduct and outcome
adjudication

Orig & amended protocol
SAP (efficacy/safety), DSMB
& adjudication charters,
meetings and deliberations
randomization list , addtl
investigator instructions

Clinical Filing Checklist for Day 45 meeting:

- Are datasets available for all pivotal trials?
- Are they reliable, transparent and traceable to the CRF?
- Do the datasets reflect the Sponsor's report of dosage, treatment arms, adequate exposure of doses and duration?
- Are the datasets in a format to allow review of patient data? Are endpoints, adverse events evaluable?
- Is the raw data available to derive the composite endpoints? Do the data allow replication of findings?
- Request data needed that is not submitted
- Pick the trial sites for audit

Clinical Filing Checklist- selected sections:

	Content Parameter
FORMAT/ORGANIZATION/LEGIBILITY	
1.	Identify the general format that has been used for this application, e.g. electronic CTD .
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?
4.	For an electronic submission , is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?
5.	Are all documents submitted in English or are English translations provided when necessary?
6.	Is the clinical section legible so that substantive review can begin?
LABELING	
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?

Clinical Filing Checklist- selected sections:

DATASETS	
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?
34.	Are all datasets to support the critical safety analyses available and complete?
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?



1997: 21 CFR Part 11 (62 FR 13430) providing for voluntary submission of regulatory records in *electronic format without accompanying paper copy*.

February 2012 : Final Rule in PDUFA V requiring e-submissions in standard format

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Standardized Study Data

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.



- From **FDA.GOV** - Search “**electronic submissions guidances**” and click on first result

U.S. Department of Health & Human Services www.hhs.gov

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- [Electronic Submissions](#)**
- [FDAAA \(Food and Drug Administration Amendments Act\)](#)

Electronic Submissions

Below is a sortable listing of Electronic Submissions Guidances

Category	Title	Type	Date
	Part 11, Electronic Records; Electronic Signatures — Scope and Application (PDF - 215KB)		
Electronic Submissions	Indexing Structured Product Labeling (PDF - 59KB)	Final Guidance	06/02/08
Electronic Submissions	Providing Regulatory Submissions in Electronic Format — Content of Labeling (PDF - 28KB)	Final Guidance	04/20/05
Electronic Submissions	Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing (PDF - 123KB)	Final Guidance	05/28/09
Electronic Submissions	Providing Regulatory Submissions in Electronic Format -Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (PDF - 133KB)	Final Guidance	06/11/08
Electronic Submissions	Providing Regulatory Submissions in Electronic Format, General Considerations (PDF - 54KB)	Final Guidance	01/01/99
Electronic Submissions	Providing Regulatory Submissions in Electronic Format - General Considerations (PDF - 288KB)	Draft Guidance	10/01/03
Electronic Submissions	Providing Regulatory Submissions in Electronic Format – Postmarketing Individual Case Safety Reports (PDF - 107KB)	Draft Guidance	06/12/08

How will CDISC standards help the clinical reviewer?

- Predictability across submissions - information will be where you expect it to be, and variables will mean the same. For example:
 - Outcomes
 - Demographics
 - Adverse events
 - Concomitant meds (WHO drug dictionary)
- Higher quality data (CDISC)
 - Increased transparency in the review process
 - Data omissions are evident
- Identify issues early in review period
 - Domain names may be unfamiliar and variable names non-standard (e.g.: PTNO for USUBJID).
- Validation of study results facilitated by standard analytics using new review tools



Drugs

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Development & Approval Process (Drugs)
Forms & Submission Requirements
Electronic Submissions to CDER
CDER Data Standards Program
Electronic Common Technical Document (eCTD)
Electronic Regulatory Review
Electronic Regulatory Submissions and Review Helpful Links
Electronic Submissions Presentations
Study Data Standards for Submission to CDER
Data Standards Manual (monographs)

Study Data Standards for Submission to CDER

CDER strongly encourages IND sponsors and NDA applicants to consider the implementation and use of data standards for the submission of applications. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. These resources are intended to assist submitters in the preparation and submission of standardized study data to CDER. This webpage will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

- **CDER Data Standards Common Issues Document (PDF - 115KB)** - The goal of this document is to communicate general CDER preferences and experiences regarding the submission of standardized data to aid sponsors in the creation of standardized datasets. The document is not intended to replace the need for sponsors to communicate with review divisions regarding data standards implementation approaches or issues, but instead, it is designed to compliment and facilitate the interaction between sponsors and divisions.
- **Study Data Specifications (v1.6) (PDF - 199KB)** - Study specifications for submitting animal and human study datasets in electronic format
- **CDISC Study Data Tabulation Model (SDTM)**
 - **SDTM Implementation Guide for Human Clinical Trials (SDTM IG)** - Developed by the Clinical Data Interchange Standards Consortium (CDISC), the SDTM IG is an implementation of the SDTM for clinical study data. The conceptual model and SDTM IG can be obtained from the CDISC web site at: <http://www.cdisc.org/sdtm>
 - **Standard for Exchange of Nonclinical Data Implementation Guide (SEND IG)** - Developed by the Clinical Data Interchange Standards Consortium (CDISC), the SEND IG is an implementation of the SDTM for data collected from animal toxicology studies.
 - The production version of the SEND Implementation Guide (IG) Version 3.0 (SEND IG v3.0) is NOW available at <http://www.cdisc.org/send>
- **CDISC Analysis Data Model (ADaM)** - Developed by the Clinical Data Interchange Standards Consortium (CDISC), ADaM is an analysis dataset standard accepted by CDER. The Model and Implementation Guide can be obtained from the CDISC web site at: <http://www.cdisc.org/adam>

Technical Assistance

- Questions regarding datasets should be forwarded to the CDER eDATA team at cdere-data@fda.hhs.gov.

Annotated CRF

Domain names of datasets relevant to this CRF page

[DM] [AE] [CO] [RELREC] [SUPPAE]

@: ADVERSE EVENTS ? @@: CUM_PGS

Patient 2000 **SUBJID**

Investigator

0248_0524 **STUDYID**

Pivotal study in early PD patients (RDC Trial)

Date of visit CUM_PGS Page 1.1.1

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AETERM ADVERSE EVENTS **AEENRF = "AFTER"**

1. Event **AEACN** Start date **AESTDTC**

AESV AE ongoing? C=cont **AECONTRT** End date **AEENDTC**

Intensity **AEOUT** Outcome Causal relationship

Serious **AEREL**

Comment **COVAL where IDVAR = AESEQ** AE-CT identification number

RELID where IDVAR = AESEQ, CMSEQ

SUPPAE.QVAL where QNAM = "AEFUP"

AESDTH where 1

AESLIFE where 2

AESDISAB where 3

AESHOSP where 4,5

AESCONG where 6

AESMIE where 7

Start date

End date

Outcome

Causal relationship

AE-CT identification number

AEs at end of trial F-up satisfactory

Variable names relevant to this CRF page

Conclusions

- Adequate and well controlled studies are the basis for a successful NDA; planning starts in IND
- Adequate evidence is rooted in science, codified in regulation, validated in review, described in label
- GCP is reflected in quality submissions; standards facilitate labeling of efficacy and safety



Thanks!

Slides from colleagues and OND/CDER training